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Internal Mammary Chain Sentinel Lymph Node Identification in Breast Cancer

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Background and Objectives: Sentinel lymph node (SLN) biopsy is not usually performed with respect to the internal mammary lymph node chain. However, the SLN may be located in the internal mammary chain, particularly with medial lesions. We carried out this study to investigate whether lymphatic mapping and SLN biopsy can detect internal mammary involvement in patients with breast cancer.
Methods: A dye- and gamma probe-guided SLN biopsy was performed in a consecutive series of 41 patients with tumor in situ or clinical stage I or II breast cancer. After the biopsy, these patients underwent either a modified radical mastectomy or breast-conserving surgery including axillary lymph node dissection. Biopsy of internal mammary lymph nodes was performed in 19 of these patients.
Results: No involvement of internal mammary lymph nodes was found histologically in 5 patients in whom lymphatic flow or a "hot nodule" in the internal mammary chain was found using lymphoscintigraphy. Nodal involvement was demonstrated histologically in only 1 of 5 cases where lymphatic vessels showed dye staining or faintly stained nodes. Internal mammary lymph node biopsy also was performed in 14 of 36 patients with neither stained lymphatic vessels or nodes, nor with lymphatic flow or a hot nodule by lymphoscintigraphy. Nodal involvement was found histologically in 1 of these patients.
Conclusion: SLN biopsy guided by lymphatic mapping is unreliable for identifying metastases to internal mammary lymph nodes.
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KEY WORDS: **lymphatic mapping; scintigraphy; dye-injection method; lymphatic metastases; biopsy**

INTRODUCTION

A sentinel lymph node (SLN) is the lymph node in a given lymphatic drainage group that is first to receive lymphatic flow from a primary tumor site. This node should be the first to become involved by metastasis from the tumor. Therefore, the histologic status of the SLN should be highly predictive of metastatic involvement of the lymph node group in which it is situated. A tumor-negative SLN virtually excludes involvement of regional lymphatics. SLN biopsy has been developed to assess axillary nodal status accurately without removing most axillary contents, thus avoiding unnecessary axillary lymph node dissection in patients without axillary involvement [1]. Recently, support has increased for use of SLN biopsy in staging patients with primary breast cancer [2–4]. SLN biopsy is expected to rapidly become a standard treatment option for all patients with early-

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TABLE I. Clinicopathologic Profiles of Patients Who Underwent Sentinel Lymph Node Biopsy

Characteristic	No.*	Characteristic	No.*
Age (years)	53 ± 13 (30 to 86)	Tumor size (mm)	22 ± 13
Menopausal status		Tumor location	
Pre-	22	Centromedial	16
Post-	19	Lateral	25
Clinical tumor size		Histologic type of tumor	
T0-1	21	Noninvasive ductal carcinoma	4
T2	20	Invasive ductal carcinoma	34
Clinical nodal status		Other invasive type	3
N0, N1a	34	Operative procedure	
N1b	7	Modified radical mastectomy	16
Biopsy technique of primary tumor		Breast-conserving	25
Surgical biopsy	10		
Needle aspiration and/or core biopsy	31		

*Unless specified otherwise.

stage breast cancer and will replace axillary dissection for many patients [4,5].

However, SLN biopsy usually has not been performed for the internal mammary lymph node chain [6] because internal mammary dissection generally has been abandoned [7]. Moreover, intraoperative lymphatic mapping using either radiocolloid or dye may not reliably visualize the SLN among the internal mammary lymph nodes. While little attention now is paid to the status of internal mammary nodes in the management of breast cancer [8], the primary sites of lymphatic drainage of breast carcinoma include the internal mammary as well as axillary lymph node groups. The involved SLN may be located in the internal mammary chain, particularly with medially located lesions [9], and internal mammary nodal status remains important in estimating the prognosis of patients with breast cancer [8,10–12].

Limited ability to map the internal mammary nodal group is considered an important drawback of the SLN biopsy approach to assessment [9]. Recent developments in sentinel node techniques may facilitate selective removal of internal mammary lymph nodes in patients with breast cancer [13]. In the present study, we investigated whether lymphatic mapping to guide SLN biopsy could detect internal mammary node involvement in 41 patients with breast cancer.

MATERIALS AND METHODS

Patients and Treatment

After informed consent was obtained, SLN biopsy was performed in a consecutive series of 41 patients with tumor in situ or clinical stage I or II breast cancer by the TNM classification [14] in the Second Department of Surgery at Kanazawa University Hospital between March 1998 and February 1999. We excluded patients whose primary tumor exceeded 5 cm in greatest diameter (T3) and those with involved axillary nodes fixed to one another or to other adjacent tissue (N2). However, patients with palpable axillary nodes (N1a, N1b) were included because clinical evaluation of axillary nodes in these patients frequently is inaccurate [15]. Patients with in situ disease also were included because microinvasion and lymph node metastases sometimes proves significant in these patients [15,16].

The average age of the patients was 53 years (range, 30–86). Twenty-two patients were premenopausal and 19 were postmenopausal; 21 patients had T0 or T1 and 20 patients had T2 primary lesions. Thirty-four patients had clinically negative nodes (N0, N1a) and 7 had clinically positive nodes (N1b). Tumors were located centromedially in 16 cases and laterally in 25. Ten patients had undergone a surgical biopsy previously. In the remaining 31 patients, preoperative diagnosis had been made by fine-needle aspiration (FNA) and/or needle core biopsy. After sentinel lymph node biopsy, these patients underwent either a modified radical mastectomy or breast-conserving surgery including a complete axillary lymph node dissection (levels I to III). Modified radical mastectomy was performed in 16 patients, while breast-conserving surgery was chosen in 25 patients. Subsequently, biopsy of internal mammary lymph nodes was performed in 19 patients, including patients with centromedially located lesions ($n = 13$) or laterally located disease ($n = 3$) who underwent modified radical mastectomy and those with medially located lesions who underwent breast-conserving surgery ($n = 3$) (Table I).

Identification of Sentinel Lymph Nodes

The technique of combining dye- and gamma probe-guided methods (the two-mapping procedure) has been described elsewhere [6]. These methods were modified in the present study as follows. Two hours before surgery, 3 mCi of 99m technetium-labeled human serum albumin (99mTc-HSA; particle size: 2–3 nm; Dai-ichi Radioisotope Institute, Tokyo, Japan) in 0.3 mL of saline were injected at 3 points into the peritumoral area. Planar

scanning of involved breast, axillary, and internal mammary areas in the anterior projection was performed 30 min after radiotracer injection. After induction of general anesthesia, patent blue dye (CI 42045; Wako Pure Chemical Industry, Osaka, Japan) was injected at 4 points around the tumor or biopsy site in the breast, using a 25-gauge needle, 10–15 min prior to the surgical procedure. A gamma-detection probe (C-trak; Care-Wise Medical, Morgan, CA, or Navigator; USSC, Norwalk, CT) was used to confirm the location of the SLN and to guide the dissection when the afferent lymphatic vessels were difficult to identify.

Internal Mammary Node Biopsy

The technique of internal mammary lymph node biopsy has been described in detail elsewhere [12,13]. The pectoralis muscle was split in the direction of its fibers over the first and second intercostal spaces. The intercostal muscles were dissected from the superior border of the rib cartilage, and the underlying mediastinum and pleural reflection were exposed. The internal mammary vessels usually were seen, and the internal mammary lymph node was found just behind the superior border of the cartilage and the sternum. The internal mammary lymph nodes were gently dissected away from adjacent vessels and pleura, and then the pectoralis muscle was sutured before skin closure.

Histologic Examination

Resected breast tissue. The size of the tumor in the resected breast tissue was recorded. Then the resected specimen was fixed in 10% formalin and examined histologically after hematoxylin and eosin (H&E) staining of paraffin-embedded sections. The histologic tumor type was determined according to the Histological Classification of Breast Cancer proposed by the Japanese Breast Cancer Society [17], a modification of the Histological Types of the World Health Organization [18]. The tumors were classified histologically into 3 major types: noninvasive ductal carcinoma, invasive ductal carcinoma, and other types of invasive carcinoma.

Sentinel lymph node specimens. SLNs were bisected and their cut surfaces were touched to clean slides that then were dried and stained by the May-Giemsa method and by anticytokeratin antibody (MAS 494; Harlan Sera-Lab, Loughborough, England). The SLN then was frozen and sections were cut and stained with H&E. The remaining frozen tissue block was thawed, fixed in 10% formalin, and processed routinely for paraffin sections with H&E staining. If no tumor was identified using H&E staining, cytokeratin immunohistochemical (IHC) staining was performed on 1 section. Thus, 2 permanent sections were examined for each tumor-free SLN: 1 stained with H&E and 1 stained for cytokeratin with IHC.

Axillary lymph node dissection specimens. Axillary lymph node specimens were dissected fresh and processed using routine surgical pathology techniques for isolation of lymph nodes. The number of dissected axillary lymph nodes was recorded. The nodes then were bisected and embedded in paraffin blocks and examined histologically with H&E but not with IHC staining.

Internal mammary lymph node biopsy specimen. The internal mammary lymph node specimens were frozen, and sections were cut and stained with H&E. The remaining frozen tissue sections were thawed, fixed in 10% formalin, and processed routinely for paraffin sectioning for H&E but not for IHC staining.

RESULTS

Tumor Histology and Regional Lymph Node Metastases

Histologic types of tumor were identified as noninvasive ductal carcinoma in 4 cases, invasive ductal carcinoma in 34, and other types of invasive carcinoma in 3. The mean tumor diameter was 22 ± 13 mm (Table I). The overall incidence of axillary metastases was 37% (15/41), while no axillary metastases were found in 4 patients with noninvasive ductal carcinoma. On the other hand, internal mammary lymph node metastases were found only in 2 of 19 patients (11%) who underwent biopsy of internal mammary lymph nodes.

Sentinel Lymph Node in the Axillary Lymph Nodes and Axillary Lymph Node Dissection

The SLN was identified successfully among axillary lymph nodes in 37 of 41 patients (90%). On the examination of permanent sections, SLN contained metastases in 13 of the 37 patients. In 5 patients, the SLN was the only node involved, while in the remaining 8 patients other axillary nodes also were positive. In 2 of the 37 patients, the SLN was falsely negative, meaning that no tumor was identified in the SLN but at least 1 nonsentinel node harbored a metastasis. Consequently, a diagnostic accuracy of 95%, a sensitivity of 87%, and a specificity of 100% were achieved in the diagnosis of axillary metastases. A diagnostic accuracy of 100%, a sensitivity of 100%, and a specificity of 100% were achieved in patients with breast cancers less than 1.6 cm in largest diameter.

Sentinel Lymph Node and Biopsy of the Internal Mammary Lymph Nodes

In 5 of 41 patients (12%), lymphatic flow and/or a hot nodule in the internal mammary chain was found preoperatively using lymphoscintigraphy, although no hot nodule was detected intraoperatively using the gamma probe. Internal mammary lymph node biopsy was performed in these patients, but no internal mammary lymph node metastasis was found histologically. Internal mammary

TABLE II. Lymphoscintigraphic Findings and Nodal Biopsy in the Internal Mammary Chain

Internal mammary node (IMN) visualization	No. of cases	IMN biopsy	Histologically confirmed IMN involvement
Lymphatic flow only	3 (8%)	3	0
Lymphatic flow and hot spot	2 (4%)	2	0
No lymphatic flow or hot spot	36 (88%)	14	2
Total	41	19	2

TABLE III. Dye Staining and Nodal Biopsy in the Internal Mammary Chain

Internal mammary node (IMN) visualization	No. of cases	IMN biopsy	Histologically confirmed IMN involvement
Faintly stained node	3 (7%)	3	0
Stained lymphatics	2 (5%)	2	1
No stained node or lymphatics	36 (88%)	14	1
Total	41	19	2

lymph node biopsy also was performed in the 14 of 36 patients without lymphatic flow or a hot nodule; involvement was present histologically in 2 of these patients (Table II). On the other hand, stained lymphatic vessels and/or faintly stained nodes were found intraoperatively in 5 patients. When internal mammary lymph node biopsy was performed, involvement was found histologically only in 1 of these patients. Internal mammary lymph node biopsy also was performed in 14 of 36 patients without stained lymphatic vessels and faintly stained nodes, and involvement was found histologically in 1 patient. This patient had no staining or hot nodules in axillary lymph nodes and no axillary lymph node metastases (Table III).

DISCUSSION

The primary sites of lymphatic drainage for breast carcinoma are the axillary and internal mammary lymph nodes. Although the axillary nodes are found more frequently to contain metastases, internal mammary node metastases prove to be present in approximately 20% of patients with operable breast cancer [7,10]. However, several prospective randomized clinical trials have shown that the addition of routine internal mammary node dissection to radical mastectomy does not improve outcome [7] (K. Yoshimoto, The Cancer Institute Hospital, Tokyo, Japan, personal communication). However, one study suggested that internal mammary node involvement has some bearing on prognosis, with patients harboring positive nodes in both the axillary and the internal mammary chains having the worst overall survival rate [10]. Because extended radical mastectomy is associated with considerably greater morbidity than standard radical or modified radical mastectomy, less aggressive internal mammary node biopsy techniques have been advocated by some authors [10,12]. In the present study, biopsy of internal mammary lymph nodes was performed in the first and second intercostal spaces [19]. We found internal mammary lymph node metastases in only 2 of 19 patients (11%). This frequency was equivalent to that detected by a standard internal mammary lymph node dissection in a previous study, in which metastases were found in 14 of 130 patients (11%) with in situ, stage 1, and stage 2 breast cancer [20]. However, a routine biopsy of internal mammary lymph nodes can be both technically cumbersome and subject to sampling error [11]. Such methods have not been widely adopted, given the seemingly random nature of such biopsies and the relatively low incidence of metastatic disease.

The SLN most often is located in the axilla [21], and SLN biopsy has been developed to assess the axillary lymph nodes accurately. In the present study, a sensitivity of 100% was achieved in patients with breast cancers less than 1.6 cm in largest diameter, indicating that axillary lymph node dissection may be avoided in these patients if no metastases are histologically evident in the SLN. However, the SLN may be located in the internal mammary chain, particularly with medial lesions [9], and selective sampling of the internal mammary lymph nodes may be needed for complete staging. Ongoing development of sentinel node techniques ultimately may make removal of internal mammary lymph nodes selective rather than random [13]. However, dissecting out blue-stained lymphatic vessels and nodes in the internal mammary chain can be difficult. In the present study, biopsy of the internal mammary lymph nodes was performed after resection of primary tumor and axillary lymph node dissection. Consequently, blue dye did not allow visualization of internal mammary nodes in most patients, while stained lymphatic vessels and/or faintly stained nodes were found intraoperatively in only 5 patients. The blue dye travels rapidly through the lymphatic vessels

TABLE IV. Reported Identification of Sentinel Lymph Nodes (SLN) in the Internal Mammary Chain

Method/reference	No. of patients	Tracer	Identification of SLN (%)
Lymphoscintigraphy			
Uren et al. [26]	34	^{99m}Tc-antimony sulfide	12 (35%)
Roumen et al. [27]	83	^{99m}Tc-colloid albumin	2 (2%)
O'Hea et al. [28]	56	^{99m}Tc-sulfur colloid	6 (11%)
Pijper et al. [29]	37	^{99m}Tc-colloid albumin	5 (14%)
Gulec et al. [30]	74	^{99m}Tc-sulfur colloid	3 (4%)
Gamma-probe method			
Harlow et al. [13]	680	^{99m}Tc-sulfur colloid	34 (5%)

and may not always remain in the internal mammary lymph nodes sufficiently long enough for surgical identification and excision.

Previously, internal mammary lymphoscintigraphy has been used in attempt to diagnose nodal metastases [19,22] and to locate the internal mammary nodes for planning of radiotherapy [23,24]. Therefore, SLN may be visualized in the internal mammary chain in preoperatively obtained lymphoscintigraphic images [25], as described in several recent studies on SLN biopsy. Table IV shows data from our literature review concerning lymphatic mapping and sentinel lymph node biopsy in the internal mammary chain. Using lymphoscintigraphy, Uren et al. [26] have reported unexpected drainage across the centerline of the breast to either the axillary lymph nodes or internal mammary lymph nodes in 32% of patients with inner or outer quadrant lesions; 9 of the 34 patients had an SLN in the internal mammary chain. The other authors also have identified internal mammary SLN [27–29] (Table IV). In these studies, however, internal mammary nodes were not removed at operation, so presence or absence of metastases in the chain could not be confirmed. Exceptionally, Gulec et al. [30] have reported that 3 of 74 SLN (4%) were situated in the internal mammary chain with no metastases being found in these nodes (Table IV). While lymphatic flow or hot spots were observed in 5 of 41 patients (11%) in the present study, no internal mammary lymph node metastasis was found histologically in these patients.

At the other extreme, using a handheld gamma probe, Harlow et al. [13] found extra-axillary hot spots in 44 of 680 patients (6.5%); they were located in the internal mammary nodes in 34 of their patients, while extra-axillary involvement was confirmed histologically in only 3 of 44 patients (Table IV). This frequency is considerably lower than those determined with radioactive colloidal gold [31]. In the present study, no definite hot nodules were detected by the gamma probe using 99m-technetium human albumin. Such variation suggests that tracer kinetics may have a major impact on feasibility of SLN biopsy. Human serum albumin with a molecular size below 50 nm is probably too small to accumulate selectively and persistently in SLN. With small particles such as the 99m-Tc antimony sulfide used by Uren et al. [26], the risk of sampling nonsentinel nodes increases over time. Paganelli et al. [32] advocated use of only larger tracers (particle diameters between 200 nm and 1000 nm) for identifying the SLN. Further attempts to identify the SLN among the internal mammary lymph nodes using the gamma probe should be made. Frequency and significance of SLNs in the internal mammary chain need to be elucidated.

Currently, internal mammary SLN biopsy is sometimes recommended for medially placed tumors < 1.0 cm when either lymphoscintigraphy or the intraoperative gamma probe method suggests internal mammary drainage of isotope [3]. Based on pathologic findings following internal mammary lymph node dissection in patients with breast cancer, however, very small lymph nodes are present in the internal mammary chain [33]: Limited accumulation of isotope in these minute nodes would not be detected by lymphoscintigraphy or the gamma probe. Effacement of regional nodes by gross tumor involvement also may adversely affect both the localization rate and predictive value of SLN biopsy [34]. In some cases, moreover, tumor within lymphatic channels may affect tracer dynamics. Preoperative imaging modalities such as sonography and computed tomography may be too insensitive for decision-making regarding internal mammary SLN biopsy, and failure to identify and remove internal mammary SLN will lead to understaging. Recently, however, we began to investigate the feasibility of internal mammary SLN biopsy using larger radiotracer with a backup biopsy of internal mammary lymph nodes particularly in patients with medial lesions. If a reliable technique for identifying SLN among internal mammary lymph node is established and if metastases are found in the internal mammary SLNs, this lesion may be treated more aggressively with radiotherapy and appropriate systemic therapies.

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